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AF/1642


Docket No.: NY-LUD 5466-US7-DIV
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Elisabeth Stockert et al.

Application No.: 10/023,182 Confirmation No.: 3379

Filed: December 17, 2001 Art Unit: 1642

For: ISOLATED NUCLEIC ACID MOLECULES ENCODING ESO-1 PEPTIDES AND USES THEREOF Examiner: M. T. B. Davis

**REPLY BRIEF**
**(37 C.F.R. § 41.41)**

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Reply Brief is submitted in response to the Examiner's Answer, dated July 25, 2006.

A Reply Brief is submitted because the Examiner's Answer presents errors and misunderstandings relating to the application under consideration, and reply is thereby deemed necessary.

At page 5 of the Examiner's Answer, lines 1-3, the following is states:

> "It is noted that SEQ ID NO: 1 is a cDNA fragment of 752 nucleotides in length, encoding a fragment of the NY-ESO-1 protein, which fragment is relatively large, and thus would contain numerous peptide epitopes."

(emphasis added). It is NOT true that either the cDNA or the amino acid sequence represent fragments. The specification does not so state. In fact, page 16, lines 28-30 states:

> "The long ORF indicated that the deduced sequence of NY-ESO-1 is 180 amino acids. The single immunopositive clone contained a sequence encoding 173 of these."

The complete amino acid sequence is provided and thus, as discussed infra, the universe from which the claimed subject matter may be chosen is limited.

Whether the protein is "relatively large" or not is something applicants are not qualified to address, as the description begs the question, "relative to what?" It is agreed that numerous peptide epitopes are described.

Further, applicants disagree that "Immunoreactive portion" is undefined, as is asserted by the Examiner. The claims require a portion of the referred to protein, so it must be less than 180 amino acids. In addition, since the immunoreactive portion protein must be processed to a peptide which binds to an MHC molecule, it must be at least that large.

Page 23 of the specification incorporates certain references into the specification and in their response of April 1, 2005, applicants referred the Examiner to Marsh, et al., The HLA Facts Book. These references establish a minimum size of about 9 amino acids for T cell binders. Hence, it can be said, without reservation, that the claim does define a minimum size, and a maximum size, of the claimed molecule, and defines the reference molecule from which the fragments derive.

The Examiner then goes on to present an extensive argument regarding the fact that peptides which bind to HLA molecules do not necessarily stimulate T cell receptors.

This is not a point that Applicants are challenging. They have stated, more than once, that not every binding peptide stimulates the generation of T cells; however, what is true is that if a peptide/MHC complex is going to stimulate a T cell response, the peptide must bind to the MHC molecule. There are well defined rules for MHC binding, set forth in the references which are set forth in the specification, and incorporated therein. Applicants provide an extensive list of peptides which would be expected to bind to various MHC molecules. See, e.g., page 26 of the specification. The specification also teaches how to determine if the binding peptides stimulate T cells. References cited by the Examiner teach this as well, as elaborated upon infra.

The "bottom line" is the following. There is a binding motif for, e.g., HLA-A24, described in the cited references. Pages 25-26 show this, and its application. Applicants "walked" through the molecule, following the rules, and identified the binders. They define, and also reference methods for determining which of the binding molecules will stimulate T cells. The "structure" which the Examiner insists is so critical to satisfying written description is provided, via the combination of the known, binding motifs for MHC molecules - which does vary from MHC molecule to MHC molecule - and the defined structure of the amino acid sequence that is encoded, by SEQ ID NO: 1.

To this end, the references relied upon by the Examiner do not appear to bring anything into the case to support the Examiner's position. Stites, for example, indeed does teach that T cell receptors generally respond only to a specific combination of antigen and MHC. Applicants agree. The invention is about identifying those antigens which do complex with a type of MHC molecule, and which do cause a T cell receptor to respond. Not only do Applicants explain how to do it, they did it.

The Examiner further relies on Kirkin - a NON PRIOR ART paper - for allegedly showing that "only few peptides from melanoma associated antigens have been so far identified as being recognized by specific CTLs, and that some Melan-A/MART-1

peptides, although having high affinity for HLA-A2.1 antigen do not induce the generation of melanoma specific CTLs in vitro.

With respect to Kirkin, a few comments must be made. First, the Examiner ignores page 667, Table 1, listing 37 peptides which do in fact stimulate CTLs (including the 3 of the application under consideration). With respect to the comments regarding Melan-A/MART-1, at page 670, second column, several comments must be made.

First, Melan-A/MART-1 is NOT NY-ESO-1. Kirkin is notably absent of any critique of NY-ESO-1. Finally, notwithstanding the fact that some Melan-A/MART-1 peptides did not induce CTLs, some did. Page 670, right hand column, relied upon by the Examiner, so states, as does the Table at page 667, referred to supra.

Finally, applicants point out that they have in fact, made of record, in their Amendment of April 1, 2005, evidence of 11 additional, NY-ESO-1 derived peptides, which are in fact CTL stimulators. The Examiner dismissed this evidence by stating:

> "(T)he amino acid sequence consisting of the specific peptides cited in the references, which are published after the date of filing of the instant application, are not described in the specification, and one of skill in the art would reasonably conclude that Applicant did not have possession of the claimed genus of immunoreactive portions at the time of filing."

Applicants beg to differ. The peptide sequences they made of record are all found in the reference, NY-ESO-1 sequence (the protein encoded by SEQ ID NO: 1). The peptides satisfy binding motifs, and Applicants explained how to scan a protein for peptides which satisfy the binding motifs. How, then, can it be concluded that Applicants did not possess these at the time of filing?

The Examiner then cites a reference, which provides a definition of "epitope," and argues that Applicants do not provide adequate written disclosure to support this definition.

It is pointed out that Federal Circuit precedent specifically warns the field NOT to do what the Examiner did here. In Phillips v. AWH Corp., 75 USPQ2d 1321, 1327-1331 (Fed. Cir. 2005), the Federal Circuit expressly held that dictionary definitions, which constitute extrinsic evidence, should only be considered after the intrinsic evidence is considered fully. See Phillips at 1330:

> [W]hile extrinsic evidence "can shed useful light on the relevant art," we have explained that it is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" C.R. Bard, Inc. v. U.S. Surgical Corp., 388 F.3d 858, 862 [73 USPQ2d 1011] (Fed. Cir. 2004), quoting Vanderlande Indus. Nederland BV v. Int'l Trade Comm'n, 366 F.3d 1311, 1318 [70 USPQ2d 1696] (Fed. Cir. 2004)...
>
> Within the class of extrinsic evidence, the court has observed that dictionaries and treatises can be useful in claim construction.... Because dictionaries, and especially technical dictionaries, endeavor to collect the accepted meanings of terms used in various fields of science and technology, those resources have been properly recognized as among the many tools that can assist the court in determining the meaning of particular terminology to those of skill in the art of the invention....

The Phillips court went on to show concern that methods for claim interpretation have "placed too much reliance in extrinsic sources such as dictionaries, treatises and encyclopedias, and too little on intrinsic sources, in particular the specification and prosecution history."

In the present case, the Examiner attempts to define "epitope" and then to let this definition control claim interpretation. Phillips prohibits this.

The Examiner also cites to case law which does not support her position.

University of California v. Eli Lilly & Co., 43 USPQ2d 1398, and Enzo Biochem, Inc. v. Gen Probe, Inc., 63 USPQ2d 1609 (2002) are both cited by the Examiner, at page 7 of her Answer.

Indeed, the University of California case did state that written description "requires a precise definition, such as by structure, formula, or chemical name." As Applicants have pointed out, repeatedly, the protein encoded by SEQ ID NO: 1 has a precise structure and formula. One can visualize the members of the genus, simply by referring to the defined amino acid sequence. Applicants admit that the genus is large; however, no statute or regulation proscribes the size of a genus which may be claimed. The case would not permit claims defined only by function, but that is not what the claims at issue recite. They do recite function, but they also recite structure.

With respect to Enzo, the Examiner refers to language in the holding thereof which could not be more favorable to Applicants' position. For example, Enzo refers to "disclosed correlation between function and structure." As Applicants have pointed out, both in these appeal proceedings and in the prosecution of the application, motif analysis provides this, i.e.,:

> (i) for T cell activation, a peptide must bind to an MHC molecule, and;
>
> (ii) the rules for peptide binding to MHC molecules are well known.

Thus, it is not seen how the criteria are not met.

At page 10, the Examiner again falls into the trap of using her own definition of "epitope," rather than Applicants, and includes B cell epitopes in her rejection. As the claims do not include such molecules, i.e., the claims are limited to T cell responses, the

Examiner's inclusion of the argument in B cells is confusing, especially in view of item "B" at page 16 of the Answer.

The Examiner has presented responses to Applicants' Brief at pages 11-18. These will be addressed in turn.

First, the Examiner asserts that Applicants have misrepresented her position by stating that she fees an insufficient number of immunoreactive peptides are disclosed; however, the discussion which follows clearly support Applicants understanding of the Examiner's position.

It is pointed out, for example, that Applicants expressly state in their specification that SEQ ID NOS: 4, 5, and 6 were the best T cell stimulators, not the only ones.

The Examiner continues to argue as well that SEQ ID NOS: 4, 5, and 6 share no common structure with the claimed genus. SEQ ID NOS: 4, 5, and 6 are all amino acid sequences found in SEQ ID NO: 1, as the specification points out. They share linear features. As Applicants say nothing about conformational epitopes for T cells in their specification, and this is a fabrication of the Examiner's unwarranted imposition of a definition not presented intrinsically, this can be ignored.

With respect to the argument set forth at pages 12-14 of the Examiner's Answer, this is, essentially, a rehash of arguments presented previously, and discussed supra. Applicants will not belabor this point.

The Examiner then brings in Fiers v. Revel, Amgen Inc. v. Chugai and the "Eli Lilly" case, supra, to support the argument that claim cannot be defined by function only.

Fiers involved a case claiming a genus of nucleic acid molecules, where none were disclosed. It is simply NOT the case that no structures are defined by the claims. With respect to Eli Lilly, repeating the holding does not make it any more controlling.

At pages 16-17, the Examiner tries to distinguish what is claimed from Example 14 of the Interim Written Description Guidelines. The example sets forth a claim to molecules which share 95% sequence identity with a reference molecule.

The Examiner claims the Example does not apply because:

> "(T)he limitation of sharing 95% sequence identify, or a common structure, that correlates with the ability to elicit a T cell response, is not disclosed in the claims, or the specification."

First, the claims require 100% sequence identity to a portion of SEQ ID NO: 1. Second, there is no contention that NY-ESO-1 is an immunogenic protein. Hence, the claims, and the reference molecule, share a common function.

To the extent the Examiner's comments about what is not disclosed in the claims or specification, it is believed that the Example was NOT presented to indicate that a specific degree of sequence identity is required.

Finally, the argument over pages 17-19 of the Examiner's Answer is, again, a rehash of what has already been presented, and there is no need to repeat the rebuttal set forth previously.

For reasons set forth herein, as well as those advanced in their Appeal Brief and during ex parte prosecution, Applicants submit that the rejection of the claims under 35 U.S.C. § 112, first paragraph, for failing to satisfy the written description requirement, is in error, and should be reversed.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 50-0624, under Order No. NY-LUD 5466-US7-DIV from which the undersigned is authorized to draw.

Dated: 9/15/06

Respectfully submitted,

By _____

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Reply Brief